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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,932	05/30/2001	Lijun Wu	MPI96-027CP2RCE2M	9497

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MILLENNIUM PHARMACEUTICALS, INC.
40 Landsdowne Street
CAMBRIDGE, MA 02139

EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
11/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/870,932	WU ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *158,160-163,166,179,181-184,187,200,202-205 and 208* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *158,160-163,166,179,181-184,187,200,202-205,208* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 29 August 2007 have been entered. Claims 158, 160 – 163, 166, 179, 181 – 184, 187, 200, 202 – 205, and 208 are pending and under examination.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 29 August 2007 has been entered.

Priority

3. The effective filing date of all pending claims is 11 July 1997 for the reasons previously made of record. In the remarks filed 29 August 2007 applicant did not traverse the examiner's position that 11 July 1997 is the appropriate effective filing date. All claims require that the antibody bind to the second extracellular loop of CCR5; in the remarks filed 28 November 2005 applicant stated (p. 11, final paragraph) that claims which recite the limitation "binds to the second extracellular loop" do not receive benefit of application 08/739507, filed 28 October 1996.

New Rejections

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 200, 202 – 205, and 208 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 200, from which each of claims 202 – 205 and 208 depends, is drawn to a kit which comprises "one or more ancillary reagents suitable for detecting the presence of a complex...". The specification fails to disclose the structure of those ancillary reagents. The claim does not require that any particular reagent be present, does not require that any structure be in the ancillary reagents. All that is recited is an intended use of the ancillary reagents, namely that they could be used "for detecting the presence of a complex". The skilled artisan cannot at once envision the genus of structures encompassed by this intended use, as the specification fails to describe the reagents.

Applicant is directed to the flow chart on p. 9 of the Revised Written Description Interim Guidelines Training Materials, available on the internet at <http://www.uspto.gov/web/offices/pac/writtendesc.pdf>, which is analogous to the instant situation. Claims 200 is generic to the "one or more ancillary reagents", but neither the art nor the specification discloses a representative number of species falling within the genus. There is not even identification of any particular structure, or even of any particular function, that the claimed reagents must have. All that is required is that these structurally undefined elements be suitable for a certain application. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 158, 160, 179, 181, 200, and 202 are rejected under 35 U.S.C. 102(a) as being anticipated by Bluel (March 1997. Proc Natl Acad Sci USA 94:1925-1930) as evidenced by Information for Authors for Proceedings of the National Academy of Sciences USA, January 1997.

Bluel discloses monoclonal antibody 5C7, raised against CCR5; see p. 1925 final paragraph. While the reference is silent as to whether the antibody binds to the second extracellular loop of CCR5, as recited in claim 158, this is an inherent property of the antibody. The instant specification discloses (p. 3 line 17 – p. 4 line 4) that antibody 5C7 is has these

properties. Thus the antibody disclosed by Bluel has all the functions recited in claim 158.

While the reference by Bleul does not disclose how to make the antibody, the Information for Authors, obtained from the journal's website, specifically states that "submission of manuscripts on research using Unique Materials (e.g., cloned DNAs; antibodies...) imples that the authors will make them available to qualified researchers for noncommercial use." (see p. 2 of the Information for Authors, Journal Policies, item (*viii*). Thus while "mere naming or description of the subject matter is insufficient" evidence of enabling prior art, it is recognized that:

> A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). (MPEP § 2121.01)

In this situation, the Information for Authors from the journal in which Bleul's reference was published makes it quite clear that the authors had agreed to give the antibody to any qualified researcher. One of ordinary skill in the art could have obtained the antibody by merely requesting it. Thus, the public was in possession of antibody 5C7 before the effective filing date of the instant claims. Therefore claim 158 is anticipated.

Claim 160 is anticipated as antibody 5C7 is monoclonal (Bleul, p. 1925). Claim 179 is anticipated as Bleul teaches the antibody in PBS/1% BSA/5 mM EDTA solution. See p. 1926 first column which describes this solution as the one used in three-color flow cytometry experiments, as well as p. 1927 Figure 2 which indicates that these experiments were performed using 5C7 antibody. Claim 181 is anticipated as antibody 5C7 is monoclonal (Bleul, p. 1925). Claim 200 is anticipated as Bleul teaches the antibody with "one or more ancillary reagents suitable for detecting the presence of a complex between said antibody or antigen binding fragment and said receptor". The one or more ancillary reagents are described at p. 1926 first column, and include Quantum 26 beads as well as FITC-conjugated goat anti-mouse Ig F(ab')2. Note that "one or more ancillary reagents" is a broad term and does not require that the reagents have any particular structure. As the prior art ancillary reagents are suitable for detecting a complex, they meet the limitation of claim 200 part (b). Claim 202 is anticipated as antibody 5C7 is monoclonal (Bleul, p. 1925).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 158, 160 – 161, 163, 179, 181 – 182, 184, 200, 202 – 203, and 205 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bluel (March 1997. Proc Natl Acad Sci USA 94:1925-1930) in view of Hoxie (U.S. Patent 5,994,515, of record, issued 30 November 1999, filed 25 June 1997, claiming benefit of earlier-filed provisional applications) and as evidenced by Information for Authors for Proceedings of the National Academy of Sciences USA, January 1997.

The reasons why claims 158, 160, 179, 181, 200, and 202 are anticipated by Bleul are set forth in the rejection under 35 USC 102(a) above. Briefly, the reference discloses antibody 5C7, and the Instructions for Authors provide evidence that the authors had agreed to make the antibody publicly available. Bluel teaches that CCR5 is one of the predominant coreceptors for HIV entry (p. 1929, first column final paragraph). However Bluel does not teach chimeric antibodies as recited in claims 161, 182, and 203, or humanized antibodies as recited in claims 163, 184, and 205.

Hoxie teaches antibodies to cellular proteins which mediate HIV entry; see for example column 6 lines 20 – 45. Hoxie specifically teaches that antibodies which bind to CCR5 are suitable (column 3 lines 13 – 15), and teaches humanized antibodies as well (see for example column 6 lines 46 – 52; see also column 8 lines 24 – 31 which refer the artisan to known procedures of how to humanize monoclonal antibodies). Humanized antibodies are a type of

chimeric antibody, and therefore the disclosure of Hoxie is on point to claims 161, 163, 182, 184, 203, and 205. Hoxie teaches that the antibodies described in the patent are to be administered to human patients for treatment of HIV (column 11 lines 46 – 62). However Hoxie does not explicitly teach antibodies to the second extracellular loop of CCR5 which inhibit binding of MIP-1α, MIP-1β, or RANTES and which also inhibit HIV infection as recited in independent claims 158, 179, and 200.

It would have been obvious to one of ordinary skill in the art to modify the antibody of Bleul by humanizing it as taught by Hoxie, thereby arriving at the invention of claims 161, 163, 182, 184, 203, and 205. The motivation to do so would be to minimize immune reaction when administering the antibody to human patients. The artisan of ordinary skill would clearly understand that the mouse antibody from Bleul would likely evoke an immune response when administered to humans; therefore the artisan would be motivated to minimize the immune reaction by humanizing as taught by Hoxie. It would be reasonable to expect success, as Hoxie teaches that methods of humanizing are known to the artisan, and refers the artisan to published instructions on how to accomplish this. Additionally, it would be reasonable to expect success as Hoxie teaches that his invention includes antibodies to CCR5, and that CCR5 mediates HIV entry. As Bleul also teaches that CCR5 mediates HIV entry, and teaches a monoclonal antibody against this receptor, the two references are clearly on the same topic, thus the artisan would have a reasonable expectation of success.

7. Claims 158, 160 – 161, 163, 166, 179, 181 – 182, 184, 187, 200, 202 – 203, 205, and 208 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bluel (March 1997. Proc Natl Acad Sci USA 94:1925-1930) in view of Hoxie (U.S. Patent 5,994,515, of record, issued 30 November 1999, filed 25 June 1997, claiming benefit of earlier-filed provisional applications) and as evidenced by Information for Authors for Proceedings of the National Academy of Sciences USA, January 1997 as applied to claims 158, 160 – 161, 163, 179, 181 – 182, 184, 200, 202 – 203, and 205 above, and further in view of Rodwell (U.S. Patent 4,671,958).

The reasons why claims 158, 160 – 161, 163, 179, 181 – 182, 184, 200, 202 – 203, and 205 are obvious over Bleul in view of Hoxie are set forth in the rejection under 35 USC 103(a) above. Briefly, the reference discloses antibody 5C7, and the Instructions for Authors provide evidence that the authors had agreed to make the antibody publicly available. Hoxie teaches

treatment of patients with HIV by administering antibodies. However neither reference teaches the specific fragments recited in claims 166, 187, and 208.

Rodwell teaches that Fab and (Fab')2 fragments of antibodies are smaller than intact antibodies and have advantages related to their small size, specifically that they enter target tissues more easily; see column 15 lines 44 – 59. However Rodwell does not teach antibodies to the second extracellular loop of CCR5 which inhibit binding of MIP-1α, MIP-1β, or RANTES and which also inhibit HIV infection as recited in independent claims 158, 179, and 200.

It would have been obvious to one of ordinary skill in the art to modify the invention of Bleul by making Fab or (Fab')2 fragments, as taught by Rodwell. The motivation would be to ensure that the antibodies reach target tissues. It would be reasonable to expect success, as Rodwell teaches that this ability is a function of the size of the antibody fragments, and therefore would not be expected to be dependent upon the antigen to which they bind.

8. Claims 158, 160 – 163, 179, 181 – 184, 200, 202 – 205 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bluel (March 1997. Proc Natl Acad Sci USA 94:1925-1930) in view of Hoxie (U.S. Patent 5,994,515, of record, issued 30 November 1999, filed 25 June 1997, claiming benefit of earlier-filed provisional applications) and as evidenced by Information for Authors for Proceedings of the National Academy of Sciences USA, January 1997 as applied to claims 158, 160 – 161, 163, 179, 181 – 182, 184, 200, 202 – 203, and 205 above, and further in view of Osband (U.S. Patent 4,716,111, issued 29 December 1987).

The reasons why claims 158, 160 – 161, 163, 179, 181 – 182, 184, 200, 202 – 203, and 205 are obvious over Bleul in view of Hoxie are set forth in the rejection under 35 USC 103(a) above. Briefly, the reference discloses antibody 5C7, and the Instructions for Authors provide evidence that the authors had agreed to make the antibody publicly available. Hoxie teaches treatment of patients with HIV by administering antibodies, including human patients (see column 3 lines 41 – 46) and discusses processes of screening libraries encoding human antibodies (column 9 lines 31 – 65), although such methods are predicated on having the appropriate antibody in hand (column 9 lines 31 – 53). However neither Hoxie nor Bleuel explicitly teaches methods of making human antibodies, which is on point to claims 162, 183, and 204.

Osband teaches methods of making human antibodies which do not require administering the relevant antigen to a human patient but which are to be accomplished in vitro.

See for example Osband claim 1. The patent describes methods of making antibodies against essentially any antigen (column 2 lines 25 – 39). However Osband does not teach antibodies to the second extracellular loop of CCR5 which inhibit binding of MIP-1α, MIP-1β, or RANTES and which also inhibit HIV infection as recited in independent claims 158, 179, and 200.

It would have been obvious to one of ordinary skill in the art to modify the invention of Bleul by making Fab or (Fab')2 fragments, as taught by Osband. The motivation to do so would be to make fully human antibodies, which would be advantageous as they would elicit less of an immune reaction. Additionally, the methods of Osband would allow for production of autologous antibodies, which would likely elicit no immune reaction whatsoever. It would be reasonable to expect success, as Osband teaches the methods are applicable to essentially any antigen.

Maintained Rejections

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 158, 160 – 163, 166, 179, 181 – 184, 187, 200, 202 – 205, and 208 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 36 of U.S. Patent No. 6,528,625. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the instant case are generic with respect to the antibody whereas the claims in the '625 patent name specific monoclonal antibodies which are within the scope of the instant claims. The issued claims would anticipate the instant claims.

This rejection stands for the reasons of record. Applicant did not traverse the rejection but stated that a terminal disclaimed will be filed upon indication of allowable subject matter. As no such disclaimer has yet been received, the rejection stands.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 158, 160 – 163, 166, 179, 181 – 184, 187, 200, 202 – 205, and 208 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Li (U.S. Patent 6,025,154) in view of Li (U.S. Patent 6,759,519), Rapport (1996. Journal of Biological Chemistry 271:17161 – 17166), Combadiere (1996. Journal of Leukocyte Biology 60: 147 – 152), Samson (1996. Biochemistry 35:3362 – 3367), and Atchison (1996. Science 274:1924 – 1926), as evidenced by Wu (1997. Journal of Experimental Medicine 186:1373-1381) and Samson (1997. Journal of Biological Chemistry 272:24934 – 24941).

This rejection is maintained for the reasons of record. It is noted that the '154 and '519 patents to Li are cumulative, and reference to specific columns and line numbers is to the '154 patent unless otherwise noted. Briefly, Li teaches antibodies to a protein called human HDGNR10, which is the same as human CCR5. Li also teaches monoclonal, chimeric, human, humanized, single chain Fv, and Fab fragments (column 18 lines 1 – 36), as awell as compositions and kits comprising same (column 13). Li also teaches antibodies that bind to the extracellular region (see '519 patent, for example claims 1 and 11) and also teaches that the inhibitors of the invention, which of course include antibodies, are those that inhibit binding of chemokine ligands (see Li '154 patent, column 12 lines 1 – 28). However Li does not explicitly teach selection of the second extracellular domain as the ligand binding region, does not teach that the antibodies inhibit binding of the specific ligands MIP-1α, MIP-1β, or RANTES, or inhibit HIV infection, as recited in independent claims 158, 179, and 200.

Samson (1996), Combadiere (1996), and Raport (1996) each teach binding of ligands to CCR5 and teaches that binding activates the receptor a. See for example Combadiere 1996, p. paragraph spanning pp. 148 – 149 for identification of MIP-1α, MIP-1β, and RANTES as agonists of the CCR5 (also called CC CKR5), Samson 1996 paragraph spanning pp. 3365 – 3366 for identification of these ligands, and Raport, abstract as well as pp. 17165 – 17166. Both Raport (p. 17166) and Combadiere (p. 151) teach that these ligands are known to suppress HIV-1 entry into cells, and indicate that CCR5 is the strongest candidate for a chemokine HIV receptor. However none of the references explicitly teaches making antibodies that both inhibit ligand binding and HIV entry as recited in claims 158, 179, and 200.

Atchison teaches that the second extracellular domain of CCR5 contains is sufficient for HIV-1 entry into cells (p. 1924, third column, first complete paragraph). Additionally, Atchison provides several examples of proteins which contain the second extracellular loop of CCR5 that also allow for HIV-1 entry. See for example Figure 3; note that "2555", which has the N-terminus of CCR2 (residues 1-44) fused to the remainder of CCR5 (residues 33 – 352) allows for HIV-1 entry (see also footnote 12). While not every chimeric protein containing the second extracellular loop allows for HIV-1 entry (notably "2255", which contains this loop, does not), the reference by Atchison clearly directs the artisan of ordinary skill to the second extracellular loop as one of a very few regions which has HIV-1 coreceptor activity. See Atchison, abstract, which states that "HIV-1 entry function could be reconstituted by fusion of various individual elements derived from the extracellular region of human CCR5 onto murine CCR5." Atchison also

teaches which regions of CCR5 are responsible for ligand binding and signaling (see Figure 4 for example). However Atchison does not teach antibodies.

It would have been obvious to one of ordinary skill in the art to modify the methods of Li, who teaches making antibodies against the extracellular domains of CCR5 and selecting those that inhibit ligand binding, to select those that inhibit binding of MIP-1α, MIP-1β, or RANTES and HIV entry, with a reasonable expectation of success. The motivation to do so would be to make an antibody that can inhibit HIV entry, which could be useful as an therapeutic for HIV. It would have been reasonable to expect success, as Li teaches that those antibodies which inhibit ligand binding should be selected, and each of Raport, Combadiere, and Samson (1996) teach that MIP-1α, MIP-1β, and RANTES are ligands for this receptor. Additionally, it would have reasonable for the artisan of ordinary skill to expect success in obtaining an antibody that also inhibits HIV entry, as the references by Raport and Combadiere both teach that ligands to CCR5, which of course bind to an extracellular region, inhibit HIV entry. The expectation of success is borne out by Atchison (1996) and the post-filing references by Samson (1997) and Wu. Note that Wu specifically teaches that HIV-inhibiting activity was possessed by antibodies against the chemokine-binidng region (p. 1375 second column – 1377), which indicates that the artisan of ordinary skill would have had a reasonable expectation of success.

Applicant argues that the prior art of record indicates that the activities of HIV-1 and chemokine ligands (MIP-1α, MIP-1β, and RANTES) were dissociable, thus the artisan of ordinary skill would neither have the motivation to combine the teachings nor a reasonable expectation of success. Applicant specifically points to Atchison, who teaches a chimeric molecule that has the second extracellular loop of human CCR5 (the chimera is called "2255" and described at p. 1925 first complete paragraph) did not bind HIV-1. According to applicant, this constitutes a teaching away from the claimed invention.

Applicant's arguments have been fully considered but they are not persuasive. The examiner acknowledges that Atchison teaches that not all proteins comprising the second extracellular domain of CCR5 always allow for entry of HIV-1. However, the reference as a whole does not teach away from the importance of this region of CCR5 for HIV-1 entry. The reference clearly shows at least three other embodiments of proteins comprising the second extracellular domain which do in fact mediate HIV-1 entry ("2555", "MMHM" and "MMHH"), and concludes that "rather than a single site of interaction between HIV-1 and the coreceptor, multiple elements distributed throughout the extracellular segments appear to contribute to viral

entry." (p. 1924, third column) Taken as a whole, the reference indicates teaches the artisan of ordinary skill which regions, including he second extracellular domain, are in fact important in HIV-1 entry. While this might not be the sole region responsible, non-preferred embodiments are still prior art (see MPEP § 2122(II)). The prior art is to be considered as a whole, not in individual parts (MPEP § 2141.02(VI)).

Additionally, the references as a whole provide a reasonable expectation of success. The skill in the art of making antibodies is high (applicant's remarks filed 29 August 2007, p. 7). The references indicate that both HIV-1 entry and ligand binding are mediated by the second extracellular loop of human CCR5. The artisan of ordinary skill would have a reasonable expectation of success in making an antibody that binds to both the ligand binding and HIV-entry regions of the second extracellular loop. Although some experimentation or screening might be required obviousness only requires a reasonable expectation of success, not an absolute guarantee; see MPEP § 2143.02. While applicant is correct that the evidence of record shows that the ligand-binding region and HIV-1 entry region of the second extracellular domain of CCR5 can be dissociated under certain circumstances, the prior art, particularly Li and Atchison, guide the artisan to select the second extracellular region as one of only a few to which HIV-entry-inhibiting antibodies should be made. Given that this loop is only 30 amino acids long (see Atchison, Figure 2; see also Raport Figure 2 which shows the second extracellular loop, between TM4 and TM5, is 30 residues long), the artisan of ordinary skill would be able to make antibodies that inhibit both ligand binding and HIV-1 entry by using this small region of the protein. Therefore the rejection of record stands.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
November 13, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER